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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,725	09/04/2004	Daniel W Chan	57203(71699)	7047

49383 7590 11/09/2009

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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
11/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,725	CHAN ET AL.	
	Examiner	Art Unit	
	LEI YAO	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-13,16-19,21,24-29,31,58 and 59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-13,16-19,21,24-29,31,58 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

The request filed on 9/14/2009 for a Continued Examination (RCE) under 37 CFR 1.114 based on Application No. 10506725 is acceptable, and a RCE has been established. An action on the RCE follows.

Claims 6, 14, 15, 20, 22, 23, 30, 32-57 are cancelled.

Claims 1-5, 7-13, 16-19, 21, 24-29, 31, 58, and 59 are pending and a method of determining breast cancer by measuring at least one biomarker comprising Marker I, II, or III, are under consideration.

Previous Final Office Action (3/19/2009)

The rejections of Claims 1, 2, 4-8, 10, 11, 17-19, 21, 23, 24, 26-28, 30 and 58-59 under 35 U.S.C. 102(e) as being anticipated by Mutter et al (US Patent No. 6703204) and 103 as being unattainable over Mutter in view of Lauro et al or Gion et al are withdrawn in view of amendment to the claims by limiting the range of MWs of the markers to +/- 0.15%.

Specification

The specification is again objected to because it still contains an embedded hyperlink and/or other form of browser-executable code at page 61, last line 8, which are improper incorporation by reference. The amendment to the specification filed on 2/18/2001 eliminates only the embedded hyperlink on page 1. Applicant is again

required to check entire specification and deletes all the embedded hyperlinks and/or other form of browser-executable codes. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-13, 16-19, 21, 24-29, 31, 58, and 59 remain and are rejected under 35 U.S.C. 112, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Claims 1-5, 7-13, 16-19, 21, 24-25 and 58-59 are drawn to a method of qualifying subject having breast cancer comprising measuring at least one biomarker comprising Marker I, MW (molecular weight) about 4383, Marker II, MW about 8126 and/or Marker

III MW about 8923 daltons, and correlating the measurement with breast cancer status, wherein an increase or decrease in amount of the marker compared to a control indicates breast cancer status, the method further comprises managing subject treatment based on the disease status, and measuring the biomarker after treatment. Claims 26-29 and 31 are drawn to a method of qualifying subject having breast cancer comprising measuring a plurality of biomarkers comprising Marker I, I or III above. To satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provides an enabling disclosure of how to make and use a claimed invention. The method objective of claims is diagnosing a breast cancer by the molecular weight of protein(s) detected by SELDI. Thus, it would be expected that one of skill in the art would be able to determine a subject having or not a breast cancer by either an increase or decrease amount of at least of the biomarkers based on the MW detected by SELDI without undue experimentation.

The specification teaches that mass spectrometry protein profiles of serum specimens from stages 0-1 breast cancer were compared against those of non-cancer controls to identify potential cancer biomarkers that can detect early breast cancer (Examples 1-3). The specification further teaches that these identified biomarkers to detect breast cancer was independently tested using samples from Stage II and III cancer patients and that the top scoring peaks were BC1, BC2 and BC3 (Examples 1-3). The specification further teaches that BC1, BC2, and BC3 are Marker I, II, and III having MW 4283, 8126, and 8932 daltons detected respectively (page 3, 29-39, and example 4-5). The specification further states that analysis using the BC1, BC2 and

BC3 markers show a high sensitivity and specificity (91%) for detection of those markers.

The teaching of the specification cannot be extrapolated to enable the scope of the claims because one of skill in the art could not predicts that the broadly claimed method of qualifying breast cancer would function as claimed for the following reasons:

First, the specification does not teach the structures (whole or partial sequence) or nature of the biomarkers, marker I, II, or III (BC1, 2, or 3) recited in the claims, no indicating whether they are breast cancer specific or broadly expressed in all or at least some of the cancers. The specification has not shown that the markers of BC1, 2, and 3 are statistically significant among the breast cancers as compared to the control (table 1). For example, levels of BC3 are 0.526±0.252 in normal control, 0.999±0.193 in stage 0-I, and 1.003±0.234 in stage II-III. Considering the standard deviation, the increased amounts of the marker in the cancer patients do not seem to be significant. Searching the arts, the biomarkers named BC2 (marker II) and BC3 (marker III) are recognized as a truncated plasma complement protein, anaphylatoxin C3a, lacking the C-terminal region (Li et al., inventor of the instant application, 2005, Clinical Chemistry 51(12):2229-2235; page 2229 and 2233, provided 9/17/2007). Specifically, Li et al teaches that an independent validation of the previously identified breast cancer biomarkers (BC1, BC2, and BC3) shows that BC3 was identified as being anaphylatoxin C3a lacking the C-terminal region (i.e. $C3a_{desARG}$) and BC2 was identified as being a C-terminal-truncated form of $C3a_{desARG}$. C3 is a molecule of the human complement system that is cleaved into C3b and C3a, wherein C3a is very short lived in serum and

is cleaved immediately into the more stable $C3a_{desARG}$. Li et al. also teaches that the BC1 marker was not confirmed because previous studies (i.e. the instant specification and Li et al., 2002, Clinical Chemistry 48:1296-1304, provided 9/17/2007) showed that BC1 decrease in breast cancer, whereas Li et al 2005, teaches that an increase of BC1 was associated with the cancer (page 2231). Further, in commenting on the studies of Li et al. (2005), Diamandis (2006, Clinical Chemistry 52(4):771, provided 9/17/2007) notes that there was no difference between patients with benign breast diseases and invasive cancers for BC2 and that there was no difference among patients with benign breast disease, ductal carcinoma in situ, of invasive carcinomas for BC3 (page 771). Diamandis further states that C3 is a high abundance serum protein whose serum concentration is increased or decreased in a wide variety of clinical conditions and that proteolytic processing of peptides in circulation by peptidases are well known and it should not be surprising that the identified molecules represent modified or truncated forms of C3a (page 771). Diamandis concludes that the BC2 and BC3 markers are likely non-specific biomarkers of acute phase reactions and are likely of questionable clinical value (page 771).

Secondly, diagnosis of a cancer using SELDI purely depending on amount change of a protein detected by molecular weight is unpredictable art. Srinivas et al (Clinical Chemistry, 47(10), 1901-1911, 2001) teach that the cellular proteome is a dynamic profile and is subject to changes in response to various signals and as a part of disease progression and this occurs through a interplay of posttranslational modification, translocation, protein-protein interactions, and protein-nucleic acid

interaction (see page 1908, left column, third paragraph). Srinivas et al. teach that given the complex nature of carcinogenesis and the heterogeneous nature of cellular interaction within the microenvironment of a tumor, analysis of appropriate cell population is necessary to obtain meaningful proteomic output and screen out background noise. Srinivas et al also teach that as new protein biomarker are discovered through proteomic approaches, the necessity to validate and ultimately use them in a clinical setting increases (see page 1908, right column). Moreover, there are still challenging issues related to the design of studies to evaluate SELDI and other proteomic technology, as well as the reproducibility, sensitivity and specificity of this new technology (Jacobs et al. Molecular & Cellular Proteomics, 3.4, 355-366, 2004, see page 355, left column, and page 362, right column; Wulfkuhle et al (Nature Reviews/cancer, 3, 267-275, 2003, see Page 266, Table 1 and page 271, right column, lines 13-17, page 274, right column, lines 2-9). Jacobs et al teach that the currently available technology appears to be difficult to reproduce both within and between laboratories; this relates to issues such as the reproducibility of the presence or absence of peaks and the quantification of the height of peaks (see page 362, right column). Jacobs et al further teach that there are many potential variables and consequently possible sources of bias related to differences between cases and controls, as well as variations in sample collection, processing, and storage.

Thus given the teaching in the art that the marker I (BC1) was not validated, that the marker II (BC2) and III (BC3) were not able to distinguish between benign breast disease and cancer, that complement, C3, and C3a are levels are known to vary in

variety of clinical conditions and acute phase reactions as stated above and given the claims in an art whose nature is identified as unpredictable, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and description showing the structure of the peak or the combination thereof it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Applicant's argument:

Applicant presents several arguments, the arguments related to the rejection above is responded below.

A. Until the instant invention, the claimed markers were not recognized and the markers are repeatedly found in separated cohort of subjects using SELDI with tolerable range of +/-0.15% of the claimed value. The field of SELDI-base diagnostic relies on the ability to identify proteins by their MW repeatedly in serum samples from subjects having a particular disease (page 9).

Applicants' arguments have been carefully considered but are not persuasive. Assertion the marker detected by SELDI within the range of +/-0.15% of the claimed value is not corresponding to the teaching of the specification, e.g. example 4, table 1. The value of BC3 in the stage 0-I breast cancer patient is 0.993± sd0.193. The range is ±19% (0.193/0.993 x100), much higher than 0.15%. Although the markers (BC1-3) are first recognized in the sera of breast cancer patients by SELDI, the markers do exist in the normal individuals (see table 1, non cancer control) and Applicant at the time filing

this application has not identified the structures of the markers and the result has not been confirmed by other method. If as indicated in the later publication above, the BC1-3 indeed are the truncated forms of complement C3a, the fragments are indeed changed in the ratio in a wide variety of clinical conditions as discussed above.

B. The SELDI method of molecular diagnostic relies on pattern recognition and does not require identification of the specific peptide by sequence, even Diamandis, who questions the value of the diagnostic markers, does not question the identification of the protein. Applicant cites the comments of Petricon and Liotta on diagnostic value of analysis of peptide fragments by DELDI as "*the process that generated the clipping in the first place can arise within the uniqueness of the disease tissue microenvironment" (page 10)*.

Applicants' arguments have been carefully considered but are not persuasive. Diamandis (cited in the rejection before and above) does not question the identification of the protein because Diamandis discussed a well known protein (C3a) having been identified yeas ago. Diamandis questions whether those markers are the valid biomarker for diagnostic purpose by SELDI. The cited reference although describes that SELDI based serum proteomic pattern diagnostic for cancer detection is promising field, Petricon and Liotta did see the problems of using the method, such as variance of the method is due to Day-to Day, lot-to lot, machine-to-machine, storage and handling as well as the pool of standard samples (page 26, right col). As such, Petricon and

Liotta did indicate that diagnosis of cancer solely with SELDI is not yet matured, confirming the detected peak with the other method would be necessary.

C. The relatively large standard deviation can be reduced in assay development if the biomarker is used in clinical application. The instant invention provides a minimally invasive method to test for breast cancer. All other used methods have relatively high false positive, such as mammography, MRI, even the informative PSA marker for prostate cancer. The instant method showing 93% of breast cancer patients were correctly identified at the stages (page 10-11). The variation could be explained by number of reasons. Not all markers, even those confirmed to be associated with cancer, are effective in all cases and all subjects. For example, evaluation of the effectiveness of p53 as a prognostic factor has resulted in both positive and negative conclusions in studies (page 12).

Applicants' arguments have been carefully considered but are not persuasive. Applicant is reminded that to satisfy the requirement of 112, 1st paragraph, it is necessary that the specification provides an enabling disclosure of how to make and use a claimed invention. If the nature of the biomarker is not defined, how does one skilled in the art know to make it (either for positive or negative control)? If the variation is so high (as indicated 19% standard deviation), how does one skilled in the art know to make it for clinical diagnosis? The claimed method is purposed for human subject (claim 1), how can be "large standard deviation reduced in assay development during the biomarker is used in clinical application. Even if it is fair to compare the instant method

to the other clinical used methods for diagnosing a cancer, for example, PSA, the levels lower than 3 ng/ml indicates the normal prostate, what is the cut off value in the instant claimed method? what is the amounts of markers BC1-3 in the normal control? Regarding the argument of p53 as a prognostic factor having positive and negative conclusion in studies, each method of using different protein for diagnosing a disease having own values and parameters to be considered, p53 protein is a known protein with well recognized function. However, neither the claims nor the specification have defined the nature (function or structure) of the claimed markers I, II, or III. It is not fair to compare those markers with a well known protein or used marker for the utility.

D. Referring the training material for 112 1st enablement-diagnosis assays in USPTO: "diagnostic assay is to be construed to mean any assay that cancer is used to help diagnose a condition.... A diagnosis is typically made by evaluation the result of screening assays". The reference of Li et al 2005 (cited previously and current rejection above) states that Marker I (BC1) may be limited in its use as a stand alone marker or useful in a multi-marker panel. The reference of Diamandis is considered, but it is merely a peer reviewed in one (my) opinion.

Applicants' arguments have been carefully considered but are not persuasive. First, the training material in USPTO merely gives a general direction for the examination. The status of USC 112 1st enablement does require that the claim(s) contains subject matter for one skill in the art to make and/or use the invention. Diagnosis of human breast cancer is not a method of screening for a biomarker, is a

method of using a marker for determining human disease. Neither the application nor Applicant's argument has provided objective evidence, direction, or predictability to convince that one skilled in the art could use the claimed method without undue a quantity of experimentations. Li's reference teaches BC1 marker (Marker I) as a truncated form of complement C3a and discloses an amino acid sequence, which allows confirming the detection by other assay. The instant application describes Marker I as BC1, no further information including the structure or function of the protein has ever provided. Diamandis did points out an important fact for disappointment of using the candidate B2 and B3 markers for diagnosis of breast cancer as "have decreased or increased levels in various conditions" and states that there is not difference among patients with benign and invasive breast cancer.

Thus, Applicant's arguments have not been found persuasive, and the rejection is maintained and made again.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

. Claims 1-5, 7-13, 16-19, 21, 24-29, 31, 58, and 59 are **provisionally** rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 and 48 of copending Application No. **11662830 as evidenced by** Li et al (Clinical Chemistry 51(12):2229-2235, 2005 provided 9/17/2007) . Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claim are directed to a method of enhancing cancer treatment by administering a compound of carbohydrate comprising modified pectin in combination of another chemotherapeutic agent.

The instant claims are drawn to a method of qualifying or determining a subject having breast cancer comprising: measuring at least one biomarker having molecule weight at about 8923 daltons (Marker III, BC3) and about 8126 daltons (Marker II, BC2) in a sample from a subject and correlating the measurement with breast cancer status, wherein the method further comprises measuring a known marker CA15-3, further comprises managing subject treatment based on the status, and measuring the biomarker after treatment, wherein the sample is blood and measuring and quantifying the marker by immunoassay. The biomarkers BC3 is C3adesARG and BC2 is identified as a C-terminal-truncated form of C3adesARG as evidenced by Li et al.

The claims of Application 11662830 ('830) are drawn to a method of qualifying or determining a subject having breast cancer comprising: measuring at least one biomarkers listed in table 1 (page 9) that includes C3a-desArgΔ8 (BC2) and C3a-desArg (BC3) in a biological sample from a subject and correlating the measurement with breast cancer status, wherein the method further comprises measuring a known marker CA15-3, further comprises managing subject treatment based on the status with chemotherapeutic agent, and measuring the biomarker after treatment, wherein the sample is blood and measuring and quantifying the marker by immunoassay, wherein the method of SELDI, is absorbent surface including IMAC-Ni, bio-specific of antibody absorbent.

Both set of the claims are drawn to a method of diagnosing breast cancer by detecting at least one biomarker including BC2 and/or BC3 with SELDI (mass spectrometry) and additional a known marker CA15-3. In the '830 application, BC2 (C3a-desArgΔ8) and BC3 (and C3a-desArg having 8116 and 8926 daltons (see table 1, page 9). The markers detected in the method of diagnosing breast cancer are the same markers in both applications. Thus the two sets of the claims are drawn to the same invention and would be obvious over each other. The depending claims of '830 application encompass the detailed SELDI including IMAC-Ni and biospecific, while the instant claims do not. However, the instant specification does describe that the SELDI absorbent is biospecific absorbent or IMAC-Ni [109, 121, 123, 240, 258]. Thus, the

claims of '830 application claiming the species of SELDI would anticipate the instant claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lei Yao/
Examiner, Art Unit 1642

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643